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Spontaneous coronary artery dissection-associated takotsubo syndrome: A systematic review of case reports

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Abstract

BACKGROUND

Spontaneous coronary artery dissection (SCAD) is underdiagnosed and requires comprehensive angiographic findings. Few SCAD occurrences have a comparable clinical appearance as takotsubo syndrome (TTS) or exist simultaneously, making it challenging for clinicians to treat and manage. Case reports lack consolidated

data. We examined SCAD-TTS case reports.

AIM

To conduct a systematic review of available case reports on SCAD in order to investigate its potential association with TTS.

METHODS

SCAD-associated TTS case reports were reviewed after thoroughly screening PubMed, EMBASE, Scopus, and Google Scholar databases till January 2023. Case reports described demographics, comorbidities, imaging, management, and results.

RESULTS

Twelve articles about 20 female patients were analyzed. 30% of patients ($n = 6$, > 60 years) were elderly (mean age 56.2 ± 9.07 years, range 36-70 years). Canada has 9 cases, United States 3, Australia 3, Sweden 2, Japan, Denmark, and France 1. Only 5 reports identified emotional stressors in these cases while 4 reports showed physical triggers for TTS. Nine had hypertension, 2 had hyperlipidemia, and 1 had prediabetes. 5 patients (25%) smoked. 10 (50%) troponin-positive myocardial infarction patients reported chest discomfort. 11 (55%) of 20 instances had TTS/SCAD. 12 (60%) of 20 patients exhibited ST elevation and 3 (15%) had T wave inversion on electrocardiogram. 19/20 patients had elevated troponin. 9 (45%) of 20 people had apical akinesis with TTS ballooning on cardiac imaging. All 20 exhibited echocardiographic wall motion abnormalities. 19 (95%) of 20 coronary angiography cases had SCAD. 10 of 19 SCAD patients had left anterior descending, 2 diagonal, and 2 left circumflex coronary artery involvement. 7 of 20 patients had left ventricular ejection fraction (LVEF) data. LVEF averaged $38.78 \pm 7.35\%$. 5 (25%) of the 20 cases underwent dual antiplatelet therapy. Three (15%) of 20 cases experienced occasional ectopic ventricular complexes, Mobitz II AV block, and paroxysmal atrial fibrillation. All 20 cases recovered and survived.

CONCLUSION

Given the clinical similarities and challenges in detecting TTS and SCAD, this subset needs more research to raise awareness and reduce morbidity.

Key Words: Spontaneous coronary artery dissection; Takotsubo syndrome; Takotsubo cardiomyopathy; Systematic review; Coronary angiography; Cardiology

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Core Tip: This study highlights the coexistence and clinical similarities of takotsubo syndrome and spontaneous coronary artery dissection, therefore emphasizing the importance of further research, awareness as well as comprehensive angiographic testing for effective diagnosis and management.

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INTRODUCTION

Takotsubo syndrome (TTS), also known as "broken heart syndrome," mimics a myocardial infarction and is typically caused by an abrupt surge of stress hormones, such as catecholamines, in reaction to mental or physical stress[1]. These hormones can produce a transitory weakening of the heart's contractile cells, resulting in myocardial stunning and a specific pattern of wall motion abnormalities[2]. The exact pathophysiological process behind this syndrome is not completely understood. In addition, endothelial and microvascular dysfunction can produce abrupt constriction or spasms of the coronary arteries, resulting in reduced blood supply to the cardiac muscle and precipitating the symptoms of TTS[3]. Spontaneous coronary artery dissection (SCAD) and TTS have similar causes and prevalence. Stress causes both conditions, which affect women more. However, there are differences between these conditions. A rupture in the inner layer of the coronary artery wall can block or restrict blood flow and cause SCAD. SCAD may result from arterial defects, hormones, and genetics. TTS, a type of transient heart failure, can cause chest pain, shortness of breath, and other heart attack-like symptoms. TTS may be caused by the sympathetic nervous system's "fight or flight" response.

SCAD has been reported in patients with TTS despite these differences. Genetic, hormonal, and environmental factors may be involved. SCAD and TTS affect predominantly women, particularly postmenopausal women. There may be a hormonal component to both of these conditions. SCAD and TTS share comparable pathophysiology, symptoms, triggers,

prevalence, and etiology but have distinct prognoses. Recent studies suggest a possible link between the two. TTS and SCAD have similar symptoms and etiologies, but their prognoses and outcomes are distinct. The majority of TTS patients recover without lasting effects. Cardiogenic shock, left ventricular rupture, and malignant arrhythmias are potentially lethal conditions. Patients with TTS are more likely to experience recurrent episodes and cardiovascular complications. SCAD causes myocardial infarction, heart failure, and sudden cardiac death. The severity, location, and presence of CAD influence the outcomes of SCAD. Patients with SCAD require medication, invasive procedures, and prolonged hospitalizations. This systematic review examines the presentation, clinical features, comorbidities, investigations, therapy, and outcomes of TTS and SCAD patients. TTS patient case reports with SCAD imaging are reviewed. This review discusses the pathogenesis, causes, and potential links between these two cardiovascular disorders. The review examines patient data to identify trends that may improve the diagnosis, management, and outcomes of TTS and SCAD.

MATERIALS AND METHODS

Literature review, Screening Titles/Abstracts and Population Selection Until January 2023, a comprehensive search of PubMed/Medline, EMBASE, Scopus, and Google Scholar was conducted to identify case reports and case series linked with spontaneous coronary artery dissection SCAD and TTS using relevant keywords such as Takotsubo syndrome, Takotsubo cardiomyopathy, broken heart syndrome, apical ballooning syndrome, stress-induced cardiomyopathy and spontaneous coronary artery dissection. The search was restricted to articles written in English only and with full text.

Search strategy

The systematic review comprised case reports and case series on the clinical presentation, diagnosis, and treatment of TTS with imaging evidence of SCAD. The exclusion of studies lacking sufficient TTS or SCAD-related information or failing to meet diagnostic criteria. Before retrieving the full-text papers for further evaluation, two reviewers evaluated the abstracts and titles of identified publications. To resolve conflicts, agreement or discussion with a third reviewer was sought.

Detailed search methodology

Up to January 2023, a thorough search as shown in PRISMA flow diagram ([Figure 1](#)) was carried out in the PubMed, Scopus, EMBASE and Google Scholar databases. "Spontaneous coronary artery dissection" (in title or abstract), "Takotsubo Syndrome" OR "Takotsubo Cardiomyopathy" OR "Broken Heart Syndrome" OR "apical ballooning syndrome" OR "stress-induced cardiomyopathy" (in title or abstract), and a publication date filter from 2000 to January 31, 2023, were all included in the search strategy. Publications classified as "editorial," "review," "comment," "meta-analysis," or "systematic review" were omitted; only case reports were included.

Inclusion criteria

(1) Case studies describing the connection between TTS and SCAD; (2) Publications published from 2000 to January 31, 2023; and (3) Reports that detail the demographics, comorbidities, imaging results, management, and outcomes of SCAD-TTS cases.

Exclusion criteria

(1) Publications labeled as "editorial," "review," "comment," "meta-analysis," or "systematic review"; (2) Studies that fail to mention how SCAD and TTS are related; (3) Publications released after January 31, 2023, but before 2000; and (4) Non-English articles. The search method was designed to locate pertinent case reports that satisfy the requirements for a thorough analysis of TTS related to SCAD.

Data extraction and quality assessment

From the included studies, we retrieved patient demographics (country of origin, age, gender), presenting complaints, comorbidities, medical interventions during hospitalization, imaging findings of SCAD, management, and outcomes. Using the Joanna Briggs Institute's critical appraisal criteria for case reports, the studies' quality was appraised.

Synthesis and data analysis

It was determined that a meta-analysis was not viable due to the expected heterogeneity of the included studies. Instead, a narrative synthesis of the data with minimal descriptively pooled analysis, consisting of a systematic review and summary of findings, was performed. The clinical characteristics, imaging findings, treatment, and outcomes of TTS associated with SCAD were examined descriptively and presented in tabular format. Categorical data were displayed as numbers or percentages, whereas continuous data were displayed as means with standard deviations or medians with interquartile ranges. Excel was utilized for every descriptive statistic.

Synthesis of data

The data were synthesized by summarizing the features of the included studies, including the number of patients, gender distribution, age range, and the presence of co-morbidities. In addition, the imaging findings of SCAD, treatment, and results of TTS were presented.

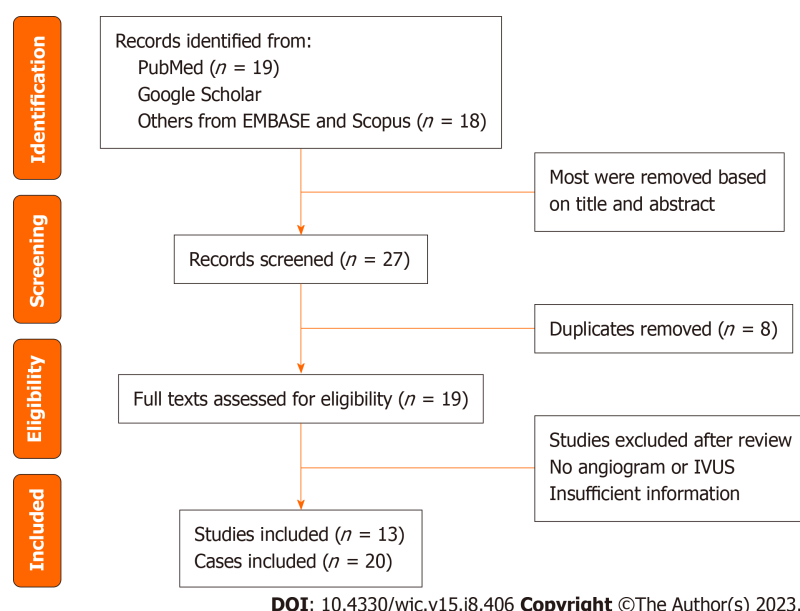


Figure 1 PRISMA flow diagram. IVUS: Intravascular ultrasound.

Quality assessment

The quality of the included studies was evaluated using the Joanna Briggs Institute's checklist for critical appraisal of case reports. Two reviewers examined the papers separately, and disagreements were resolved through consensus or contact with a third reviewer. Considering this is a systematic study of previously published case reports, ethical approval was not mandatory.

RESULTS

Twelve articles describing 20 female patients for the analysis were selected[4-15]. The mean age of the reported patients was 56.2 ± 9.07 years (range 36-70 years) out of which 40% of patients were elderly ($n = 8$, > 60 years). Out of the reported cases, 9 cases were from Canada, 3 cases each from USA, and Australia, 2 cases from Sweden and while Japan, Denmark and France contributed 1 case each. Only 5 reports identified emotional stressors in these cases while 4 reports showed physical stressors for TTS (Table 1).

Out of 20 cases, cardiovascular comorbidities were reported in 10 cases (hypertension in 9, hyperlipidemia in 2), and prediabetes in 1 case. 5 (25%) patients showed a history of smoking. The most common presenting symptom noticed was chest pain and discomfort in 9 cases (45%) and 10 (50%) cases presented with troponin-positive myocardial infarction. In 11 (55%) out of 20 cases, TTS and SCAD coexisted. Electrocardiogram was done in all 20 patients out of which 12 (60%) patients showed ST elevation and 3 (15%) showed T wave inversion. The baseline troponin level was measured in 19 cases and was elevated in all.

Out of 20, 9 (45%) cases showed apical akinesis and ballooning patterns of TTS on cardiac imaging. All 20 cases reported wall motion abnormalities on Echocardiography. In 19 (95%) out of 20 cases, SCAD was reported on coronary angiography. Out of 19 patients with SCAD, 10 showed involvement of left anterior descending (LAD) coronary artery, 2 showed diagonal artery, 2 showed left circumflex coronary (LCx) artery involvement, 2 showed marginal artery, 2 showed posterolateral artery, and a patient had a coexisting right coronary artery and LAD lesions. Out of 20 cases, data on left ventricular ejection fraction (LVEF) was reported in only 7 cases. The mean LVEF was $38.78 \pm 7.35\%$. Out of 20, 5 (25%) cases were treated with dual antiplatelet therapy. Only 3 (15%) cases out of 20 reported complications with 1 case each of occasional ectopic ventricular complexes, Mobitz II AV block, and ventricular fibrillation. All 20 cases survived and recovered (Table 2).

DISCUSSION

The coexistence of SCAD and TTS is rare and unclear[16]. The occurrence of the two is not coincidental and is mostly related to one another. SCAD was noted in many cases after a careful angiographic review of patients with TTS as the initial diagnosis[17]. SCAD rarely causes acute coronary syndrome and on the contrary, TTS shows ACS-like symptoms with left ventricular wall motion abnormality (LVWMA) without any obstructive lesions[18]. However, according to the recent update in the criteria of International Takotsubo Diagnostic criteria, TTS is diagnosed in patients with pre-existing SCAD. 2.5% of the cases diagnosed with TTS with coronary angiography (CAG) met the criteria for diagnosis of SCAD in a retrospective review.

Table 1 Baseline characteristics and presentation of cases with spontaneous coronary artery dissection and takotsubo syndrome

Ref.	Country	Age	Clinical presentation	Cardiovascular comorbidity	Prediabetes (Yes/No)	Smoker (Yes/No)
VI Chou <i>et al</i> [5], 2015	Canada	59	Troponin positive MI	Yes	No	No
VII Chou <i>et al</i> [5], 2015	Canada	60	Troponin positive MI	No	No	No
VIII Chou <i>et al</i> [5], 2015	Canada	50	Troponin positive MI	Yes	No	No
IX Chou <i>et al</i> [5], 2015	Canada	50	Troponin positive MI	Yes	No	No
Y-Hassan <i>et al</i> [14], 2016	Sweden	61	Sudden onset of chest pain	No	No	No
Ghafoor <i>et al</i> [9], 2020	United States	52	Chest pain, Palpitations	No	Yes	No
Takeuchi <i>et al</i> [13], 2021	Japan	36	Left arm discomfort and convulsions	Yes	No	No
Blazak <i>et al</i> [4], 2022	Australia	65	Severe chest pain	Yes	No	No
Y-Hassan <i>et al</i> [15], 2018	Sweden	67	Chest pain, nausea, dyspnea	Yes	No	Yes
Fitouchi <i>et al</i> [7], 2022	France	49	Retrosternal chest pain radiating to the left arm	No	No	No
Johnson <i>et al</i> [10], 2018	United States	66	Chest pain, headache, and pain in her left jaw, left arm numbness	-	-	-
Desai <i>et al</i> [6], 2020	United States	67	Chest discomfort, shortness of breath	Yes	No	No
Frederiksen <i>et al</i> [8], 2020	Denmark	57	Left arm pain, chest discomfort, dyspnea, palpitation, elevated Bp	No	No	Yes
Sugito <i>et al</i> [12], 2020	Australia	56	Central chest pain	No	No	No
McGhie <i>et al</i> [11], 2020	Australia	56	Inferior STEMI	Yes	No	Yes

Common factors which contribute to the development of SCAD include extreme physical activity, drugs, fibromuscular dysplasia, multiparity, connective tissue disorders, hormonal therapy, and inflammatory conditions[19]. The reasons for their co-existence might be because SCAD and TTS have a common predilection in younger women[10,14]. Both are preceded by significant psychological or physiological stress and share similar findings clinically. Acute chest pain caused by SCAD can trigger physical stress leading to TTS. Post-ischemic myocardial stunning caused by SCAD extending beyond the dissected coronary artery supply region resulting in the consequent LVWMA is consistent with TS. Typically, both present with ACS - chest pain, ischemic electrocardiographic abnormalities, biomarker positivity, and wall motion abnormalities that subsequently normalize.

Interestingly, TTS and SCAD have congruent diagnostic, imaging, and histopathological findings post-ischemia[19]. Patients with TTS and SCAD both report having abnormal electrocardiogram findings initially with either ST elevation, T wave inversion, or both[15,20]. In addition, although the peak values are substantially lower in comparison to acute coronary syndrome, both disorders have elevated troponin levels similar to those in acute coronary syndrome[20]. Of the 20 cases included in the study, 12 were reported with ST elevation and 3 with T wave inversion and 19 of them reported a surge in baseline troponin levels. One of the most crucial diagnostic techniques for recognizing SCAD is invasive CAG which helps distinguish SCAD in three angiographic patterns, type 1 with the presence of a double lumen, type 2 with lumen narrowing, and type 3 with abrupt lumen narrowing mimicking an atherosclerotic lesion[21,22].

Echocardiography is one the most used imaging tool where the regional wall motion abnormalities are assessed that help differentiate between these two conditions[19,20]. The regional LVWMA with a distinctive circumferential pattern is the distinguishing feature of TTS that results in the ballooning of the left ventricle during the systole, besides, the coronary artery supply regions are discordant with the LVWMA in TTS[22]. Left ventricular ballooning can be characterized by an apical, mid-ventricular, basal, or localized pattern in TTS[22]. In SCAD, main lesions are observed in the LAD and its branches rather than the right coronary artery (RCA) or left circumflex artery (LCX)[17]. However, SCAD is argued to not have classical apical ballooning observed in TTS and the wall akinesia corresponds to only the regions supplied by the affected dissected artery which leads to reversible myocardial stunning[5]. This occurs because apical ballooning, a crucial hallmark of TTS, cannot be described by the dissection in LAD as it does not wrap around the cardiac apex instead the diagonal branches, LCX and RCA, correspond to the other locations coexistent in SCAD and TTS

Table 2 Investigations, complications, and outcomes of spontaneous coronary artery dissection takotsubo syndrome cases

Ref.	ECG	Troponin elevated?	Lesion & dissection involved which vessel?	LVgram	LVEF	DAPT (Yes/No)	SCAD and TTS coexist?	Complications	Final outcome
I Chou <i>et al</i> [5], 2015	STEMI	Yes	RPLA	N/A	-	No	-	No	Survived
II Chou <i>et al</i> [5], 2015	STEMI	Yes	1st obtuse marginal and 1st Dx	N/A	-	No	-	No	Survived
III Chou <i>et al</i> [5], 2015	Antero-lateral TWI	Yes	Distal LAD	N/A	-	No	-	No	Survived
IV Chou <i>et al</i> [5], 2015	NSVT	Yes	Distal LPL	N/A	-	No	-	No	Survived
V Chou <i>et al</i> [5], 2015	Antero-lateral TWI	Yes	1st Dx	N/A	-	No	-	No	Survived
VI Chou <i>et al</i> [5], 2015	STEMI	Yes	1st mid-Dx	N/A	-	No	-	No	Survived
VII Chou <i>et al</i> [5], 2015	Antero-lateral STD, TWI	Yes	Distal LAD, 3rd Dx	N/A	-	No	-	No	Survived
VIII Chou <i>et al</i> [5], 2015	VT	Yes	Distal LAD	N/A	-	No	-	No	Survived
IX Chou <i>et al</i> [5], 2015	STEMI	Yes	Distal LAD	N/A	-	No	-	No	Survived
Y-Hassan <i>et al</i> [14], 2016	STEMI	Yes	Dx	LV apical ballooning	-	None	Coexist	No	Survived
Ghafoor <i>et al</i> [9], 2020	STEMI	Yes	RCA and Distal LAD	Apical akinesis	50-55%	Yes	Coexist	Occasional ectopic ventricular beats	Survived
Takeuchi <i>et al</i> [13], 2021	STEMI	Yes	Middle to distal LAD	Apical ballooning	39%	Yes	Coexist	No	Survived
Blazak <i>et al</i> [4], 2022	NSTEMI	Yes	Dx	Apical akinesis	28%	None	Coexist	No	Survived
Y-Hassan <i>et al</i> [23], 2018	STEMI	Yes	Peripheral marginal branch	Circular mid-apical ballooning	26%	None	Coexist	No	Survived
Fitouchi <i>et al</i> [7], 2022	Sinus tachycardia	Yes	LAD	LV apical ballooning	45%	Yes	Coexist	No	Survived
Johnson <i>et al</i> [10], 2018	STEMI	Yes	-	Apical akinesis	41%	None	Coexist	V. fib	Survived
Desai <i>et al</i> [6], 2020	STEMI	N/A	Typical TTS pattern	Apical ballooning	N/A	None	Coexist	No	Survived
Frederiksen <i>et al</i> [8], 2020	NSTEMI	Yes	-	Apical akinesis	40%	Yes	Coexist	No	Survived
Sugito <i>et al</i> [12], 2020	STEMI	Yes	Typical TTS pattern	Circular mid-apical ballooning	N/A	None	Coexist	3:1 Mobitz II	Survived
McGhie <i>et al</i> [11], 2020	STEMI	Yes	Typical TTS pattern	LV apical ballooning	-	Yes	Coexist	N/A	Survived

ECG: Electrocardiogram; STEMI: ST-Segment Elevation Myocardial Infarction; NSTEMI: Non-ST-Elevation Myocardial Infarction; TTS: Takotsubo syndrome; LV: Left ventricle; RCA: Right coronary artery; LAD: Left anterior descending (LAD), DX diagonal branches; N/A: Not applicable.

[17]. In this review, cardiac imaging revealed apical ballooning and akinesia in 9 cases (45%), and 19 (95%) out of 20 cases, were diagnosed as SCAD on CAG. In a case series by Chou *et al* [5], several of these patients (particularly those with a long wrap-around LAD artery) with implicated mid to distal LAD artery, SCAD was found to have a large-segmental akinesia comparable to typical TTS (anterolateral, apical, and inferior akinesia/dyskinesia). The authors of the case series determined that the LVWMA in these 9 patients was consistent with the regions supplied by the dissected coronary arteries, and all 9 SCAD cases were misinterpreted as TTS[22].

Furthermore, because both the SCAD and TTS present as ACS, the majority of the SCAD and TTS are treated with a similar treatment of ACS (beta blockers, aspirin, angiotensin-converting enzymes, and/or angiotensin receptor blockers, and diuretics)[5]. Although the idea of using dual platelet therapy is controversial in SCAD, it is continued to be used in concern to the presence of thrombus within the blood vessel[21]. The majority of the lesions found in both SCAD and TTS culminate in 'restitution and integrum'[15].

The spontaneous resolution of LVWMA in hours to weeks is a defining trait of TTS[23]. In contrast to TTS, where angiographic abnormalities are frequently unchanged from prior investigations, SCAD exhibits acute and dynamic angiographic findings that resolve with time[5]. Interestingly in our review of the cases series, all 20 cases survived and recovered well with only one patient undergoing cardiac intervention and 3 cases reporting complications (case each of occasional ectopic ventricular complexes, Mobitz II AV block, and paroxysmal atrial fibrillation).

Several limitations should be acknowledged when evaluating the results of this systematic review. First, the evidence is based on case reports, which are susceptible to publication bias and may not reflect all patients with SCAD-associated TTS. Second, the quality of reporting in case reports is inconsistent and may not give comprehensive data on patient characteristics, comorbidities, and management. Thirdly, the small number of cases included in this analysis limits the findings' applicability to the larger population of patients with TTS or SCAD. Lack of established diagnostic criteria for SCAD and TTS may have led to misdiagnosis or underreporting of cases. The use of different imaging modalities in different investigations may have influenced the diagnostic precision and the reporting of the findings. In the absence of a control group, it is difficult to demonstrate a causal relation between SCAD and TTS. Further research with larger, more representative samples and established diagnostic criteria is required to confirm the results of this systematic review.

CONCLUSION

In conclusion, TTS and SCAD have peculiar similarities in clinical presentation, diagnosis, imaging findings, and management, thus, are misdiagnosed often. However, because of similar precipitant factors (physical and emotional stressors), both conditions can even co-exist. The angiographic and echocardiographic findings of SCAD can help differentiate between both conditions if interpreted with the familiarity of SCAD variants. Therefore, to avoid misdiagnosis and underreporting of SCAD, there is a need for further scientific literature to bring awareness and improve uncalled morbidity in the cohort.

ARTICLE HIGHLIGHTS

Research background

Takotsubo syndrome (TTS) and spontaneous coronary artery dissection (SCAD) have similar symptoms and etiologies, but their prognoses and outcomes are distinct. This systematic review examines the presentation, clinical features, comorbidities, investigations, therapy, and outcomes of TTS and SCAD patients.

Research motivation

To examine the presentation, clinical features, comorbidities, investigations, therapy, and outcomes of TTS and SCAD patients.

Research objectives

Our objective is to conduct a systematic review of available case reports on SCAD in order to investigate its potential association with TTS.

Research methods

SCAD-associated TTS case reports were reviewed after thoroughly screening PubMed, EMBASE, Scopus, and Google Scholar databases till January 2023. Case reports described demographics, comorbidities, imaging, management, and results.

Research results

Key findings include: Elderly patients constituted 30% of the sample, with a mean age of 56.2 years. Canada had the most cases (9), followed by the United States (3), Australia (3), and other countries. Emotional stressors were identified in only 5 cases, while physical triggers were observed in 4 cases. Half of the patients experienced chest discomfort, while a quarter were smokers. Over half of the cases (55%) had both TTS and SCAD. All 20 cases recovered and had a favorable prognosis.

Research conclusions

This study highlights the coexistence and clinical similarities of TTS and SCAD, therefore emphasizing the importance of further research, awareness as well as comprehensive angiographic testing for effective diagnosis and management.

Research perspectives

Further research with larger, more representative samples and established diagnostic criteria is required to confirm the results of this systematic review.

FOOTNOTES

Author contributions: Trambadia B, Reddy SA, Chauhan S, Desai R, and Bhanushali A contributed to resources; Trambadia B, Reddy SA, Chauhan S, Desai R, and Bhanushali A, Pandey A, Odugbemi O, and Chauhan S contributed to visualization; Trambadia B, Reddy SA, Chauhan S, Desai R, Bhanushali A, Kohli M, Prakash A, Sarvepalli SR, Odugbemi O, and Reyaz N contributed to writing-original draft; Kohli M, Prakash A, Sarvepalli SR, Pandey A, Odugbemi O, Reyaz N, Trambadia B, Reddy SA, Chauhan S, and Desai R contributed to writing - review & editing; Pandey A, Chauhan S, and Desai R, and Desai R contributed to supervision; Odugbemi O, Reyaz N contributed to formal analysis; Chauhan S contributed to conceptualization, methodology, writing - original draft; Desai R contributed to conceptualization, methodology, software, writing original draft; administration; All authors have read and approved the final manuscript.

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